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Pharmacokinetic Equivalence of Biosimilar Adalimumab-aqvh and Adalimumab in Healthy Subjects

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INTRODUCTION

- **Adalimumab-aqvh (YUSIMRY™, Coherus BioSciences) has recently been approved by the US Food and Drug Administration as a biosimilar to adalimumab (HUMIRA, AbbVie); the current study was part of the evidence supporting the approval[1]**
- Adalimumab is indicated for the treatment of rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, Crohn's disease, hidradenitis suppurativa, and uveitis[2]
- The established efficacy of adalimumab has led to improvement in patient health; however, the treatment comes at a high cost, which is steadily increasing[3]
- Biosimilars, such as adalimumab-aqvh, are biologic drugs that are proven to be highly similar to the reference product but are available at a lower cost, which can ultimately improve patient treatment access and adherence[4]
- Biosimilars undergo an extensive review process to confirm there are no clinically meaningful differences in purity, potency, efficacy, pharmacokinetics (PK), and safety (including immunogenicity) between the biosimilar and the reference biologic[5]
- **The primary objective of this study was to compare the PK bioequivalence of adalimumab-aqvh and adalimumab after a single subcutaneous 40-mg dose administered to healthy subjects**
- **The secondary study objective was to assess the safety, immunogenicity, and tolerability of adalimumab-aqvh**

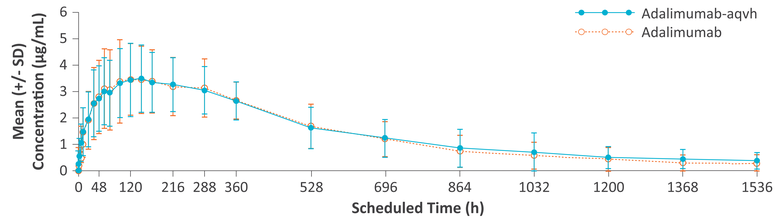
METHODS

- This randomized, double-blind, single-dose, parallel-group study was conducted with healthy adult subjects (N = 210) at 2 sites in the United States
- Subjects were randomly assigned 1:1 to receive either a single 40-mg subcutaneous dose of adalimumab-aqvh or adalimumab in a prefilled syringe
- The primary PK end points were maximum serum concentration (C_{max}) and the area under the serum concentration versus time curve extrapolated from 0 to infinity ($AUC_{0\text{-}inf}$) of adalimumab-aqvh and adalimumab. The PK evaluable population included all subjects who completed treatment and had sufficient serum PK data to calculate at least 1 of the key PK parameters (C_{max} or $AUC_{0\text{-}inf}$)
- Other PK end points were the time to reach C_{max} (t_{max}), terminal elimination half-life ($t_{1/2}$), area under the curve calculated from 0 to the last measurable concentration ($AUC_{0\text{-}last}$), and apparent volume of serum cleared of drug per unit time (CL/F)
- Treatment-emergent adverse events (TEAEs) were assessed in the safety population, which included all subjects who enrolled in the study and received a dose of study treatment
- The immunogenicity outcomes included treatment-emergent antidrug antibodies (ADAs), ADA titers, and neutralizing antibodies (NAbs)

RESULTS

- The mean adalimumab serum concentrations for adalimumab-aqvh (n = 107) and adalimumab (n = 103) were similar for both treatments (**Figure 1**)

Figure 1. Linear plot of the mean serum concentration over time



SD, standard deviation.

- PK bioequivalence was seen between adalimumab-aqvh and adalimumab as the 90% CIs for the geometric mean ratios (GMRs) for the primary PK parameters were within the predefined range (80%-125%) (**Table 1**)
- The incidences of TEAEs were similar for each treatment (**Table 2**); most TEAEs were mild or moderate in severity

Table 1. Analysis of bioequivalence based on PK parameters (PK evaluable population)

	Adalimumab-aqvh		Adalimumab			
PK parameter	n	Geometric mean	n	Geometric mean	GMR, %	90% CI for GMR, %
C_{max}, µg/mL	95	3.70	93	3.75	98.64	90.66-107.32
$AUC_{0\text{-}inf}$, h·µg/mL	91	2041.00	92	1987.72	102.68	92.23-114.31
$AUC_{0\text{-}last}$, h·µg/mL	95	1903.19	93	1882.81	101.08	91.12-112.14

t test was performed on log-transformed PK parameters. GMR was presented with adalimumab as the reference group. The ratio and 90% CIs were presented after back transformation to the original scale.

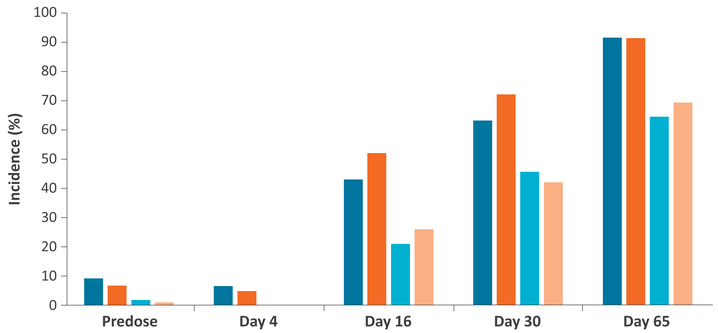
Table 2. Summary of select TEAEs (≥2 subjects in total) by system organ class and preferred term (safety population)

System organ class preferred term, n (%)	Adalimumab-aqvh n = 107	Adalimumab n = 103	All N = 210
Subjects with any TEAEs[a]	35 (32.7)	39 (37.9)	74 (35.2)
Infections and infestations	14 (13.1)	11 (10.7)	25 (11.9)
Upper respiratory tract infection	8 (7.5)	5 (4.9)	13 (6.2)
Gastroenteritis viral	3 (2.8)	0	3 (1.4)
Nervous system disorders	9 (8.4)	10 (9.7)	19 (9.0)
Headache	9 (8.4)	9 (8.7)	18 (8.6)
General disorders and administration site conditions	8 (7.5)	9 (8.7)	17 (8.1)
Injection site rash	1 (0.9)	6 (5.8)	7 (3.3)
Injection site erythema	2 (1.9)	1 (1.0)	3 (1.4)
Injection site reaction	1 (0.9)	1 (1.0)	2 (1.0)
Gastrointestinal disorders	4 (3.7)	5 (4.9)	9 (4.3)
Musculoskeletal and connective tissue disorders	1 (0.9)	7 (6.8)	8 (3.8)
Back pain	0	4 (3.9)	4 (1.9)
Skin and subcutaneous tissue disorders	6 (5.6)	2 (1.9)	8 (3.8)
Respiratory, thoracic, and mediastinal disorders	4 (3.7)	3 (2.9)	7 (3.3)
Injury, poisoning, and procedural complications	0	5 (4.9)	5 (2.4)

Percentages were calculated using the number of subjects in the column header as the denominator.
[a]TEAEs were defined as adverse events that occurred for the first time after dosing of study drug or existed before but worsened in severity or relationship to study drug after dosing.

- The proportion of subjects who had binding ADAs and NAbs increased over time in both groups; the highest proportion was seen at the end of the study (**Figure 2**). The ADA titers of treatment-emergent ADAs were comparable between the treatment groups

Figure 2. Incidence of ADAs and NAbs by visit



	Predose	Day 4	Day 16	Day 30	Day 65
Adalimumab-aqvh ADA	9.3	6.5	42.9	63.1	91.3
Adalimumab ADA	6.8	4.9	52.0	72.0	91.0
Adalimumab-aqvh NAb	1.9	0.0	21.0	45.6	64.4
Adalimumab NAb	1.0	0.0	26.0	42.0	69.0

- In both treatment groups, the occurrence of binding ADAs was associated with increased clearance, evidenced by reduced $t_{1/2}$ and increased CL/F
- Correspondingly, decreases in C_{max} and AUCs were observed in the ADA-positive groups; however, the effects were similar between the adalimumab-aqvh and the adalimumab groups (**Table 3**)

Table 3. Summary of PK parameters by treatment and ADA status (PK evaluable population)

	Adalimumab-aqvh				Adalimumab			
	ADA positive		ADA negative		ADA positive		ADA negative	
PK parameter	n	Statistic	n	Statistic	n	Statistic	n	Statistic
C_{max}, µg/mL[a]	87	3.6 (37.0)	8	5.1 (23.3)	84	3.7 (34.1)	9	4.8 (29.7)
t_{max}, h[b]	87	142.8 (36-361)	8	143.4 (72-145)	84	121.1 (36-361)	9	119.4 (48-288)
$t_{1/2}$, h[c]	83	215.0 (194.0)	8	524.7 (128.8)	83	167.7 (132.2)	9	546.5 (165.1)
$AUC_{0\text{-}inf}$, h·µg/mL[a]	83	1924.3 (44.9)	8	3760.3 (24.3)	83	1855.3 (38.1)	9	3753.6 (35.8)
$AUC_{0\text{-}last}$, h·µg/mL[a]	87	1812.4 (44.5)	8	3238.4 (21.1)	84	1781.9 (40.8)	9	3149.1 (30.9)
CL/F, mL/h[c]	83	22.9 (11.9)	8	10.9 (2.6)	83	23.1 (8.9)	9	11.3 (4.0)

[a]Geometric mean (geometric CV%) = $100 \cdot (\exp(SD^2) - 1)^{0.5}$, where SD is the standard deviation of the log-transformed data.
[b]Median (minimum-maximum).
[c]Mean (SD).

CONCLUSIONS

- **PK bioequivalence was demonstrated between adalimumab-aqvh and adalimumab after a single 40-mg dose in healthy subjects**

- The safety profile of adalimumab-aqvh was consistent with the known safety profile of adalimumab, TEAEs were comparable between the treatment groups, and no new safety signals were identified
- The occurrence of treatment-emergent ADAs and NAbs was comparable between the treatment groups, with no clinically meaningful differences
- The PK bioequivalence in the current study, combined with the similar safety and efficacy of adalimumab-aqvh in patients with psoriasis in a previous study (NCT02489227), indicates that there are no clinically meaningful differences between adalimumab-aqvh and adalimumab

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DISCLOSURES

Barbara Finck, Hong Tang, Francesca Civoli, Suzanna Tatarewicz, and Hillary O'Kelly are employees of and own stock in Coherus BioSciences (Redwood City, CA).

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